Assessment of 1,3-Butadiene Epidemiology Studies

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Positive carcinogenicity studies in mice and rats have led to concerns that 1,3-butadiene may be carcinogenic in humans under exposure conditions that have existed in occupational settings and perhaps exist today. The principal settings of interest are the styrene-butadiene rubber (SBR) manufacturing industry, which uses large quantities of 1,3-butadiene, and the 1,3-butadiene monomer industry. The potential for 1,3-butadiene exposure is highest during monomer transfer operations and is lowest in finishing areas of polymerization plants where the polymer products are processed.

Three large cohort mortality studies have been conducted in the SBR and monomer producing industries since 1980. These studies, which examined the mortality experience of over 17,000 men employed in one monomer and 10 SBR facilities, are the subject of this review. All but one of the facilites began operations during the early 1940s. The mortality experience observed within these employee cohorts is comparable to that seen in other long-term studies of men employed in the petroleum, chemical, and rubber industries for all causes of death, total malignant neoplasms, and for the specific cancers seen in excess in the toxicologic studies.

This paper discusses discrepant findings observed in more detailed analyses within individual cohorts and among employment subgroups, as well as selected limitations of the particular studies. Additional efforts to refine 1,3-butadiene exposure categories are needed. Within the context of sample size limitations inherent in these studies, there is currently inadequate evidence to establish a relationship between cancer mortality outcomes and 1,3-butadiene exposure in humans.

Assessment of 1,3-Butadiene Epidemiology Studies

Both toxicologic and epidemiologic studies have led to concerns that 1,3-butadiene may be carcinogenic in humans (1–4). The existing literature on this subject was reviewed by the International Agency for Research on Cancer (IARC) in 1985 (5). On the basis of that review, IARC concluded that sufficient evidence did exist to classify 1,3-butadiene as a carcinogen in experimental animals. IARC concluded that there was inadequate evidence for the carcinogenicity of 1,3-butadiene in humans.

The epidemiologic literature available in 1985 was limited, consisting of several studies conducted in the rubber industry and one study of two styrene-butadiene polymerization facilities (3,4). The rubber worker study by McMichael et al. (3) is mentioned because a small styrene-butadiene polymerization facility was included among the facilities surveyed. The potential for exposure to 1,3-butadiene is very low in finished rubber products manufacturing.

Since 1985, two large epidemiologic studies have been reported that specifically examined the long-term health experience of 1,3-butadiene exposed individuals (6,7). Given these additional studies, both of which have been updated at this symposium, it is appropriate to revisit the question of the adequacy of evidence for or against the human carcinogenicity of 1,3-butadiene.

History of the Industrial Processes Studied

The three studies that most specifically address the potential carcinogenic effects of 1,3-butadiene examined the mortality experience of employees from one Canadian and nine U.S. synthetic rubber manufacturing plants and a major 1,3-butadiene production facility (4,6,7). The synthetic rubber industry grew rapidly during the 1940s and matured quickly from a technological viewpoint. The dramatic growth was spurred by the threatened cutoff of natural rubber supplies during World War II (8). The technological maturity of the industry was advanced by the cooperative research efforts among the various producers and the U.S. government during the 1940s.

The major product of the industry was styrene-butadiene rubber polymer (SBR). The ratio of 1,3-butadiene to styrene used in manufacturing SBR was approximately 75 parts 1,3-butadiene to 25 parts

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styrene. Other synthetic rubbers were also manu-factured in lesser quantities. These included poly-butadiene rubber and rubbers based on polymers of 1,3-butadiene and acrylonitrile. SBR production was initiated in 1942. Production volumes reached 181,000 metric tons in 1943 and increased to 714,000 metric tons by 1945 (9). U.S. production peaked at about 1,398,000 metric tons in 1978 and thereafter has declined to 735,000 metric tons.

Large quantities of 1,3-butadiene were required for the synthetic rubber industry. Consequently, 1,3-bu-tadiene production expanded in parallel with SBR pro-duction. 1,3-Butadiene has been produced by several methods including the dehydrogenation of n-butane, the catalytic dehydrogenation of n-butene, and the extrac-tive distillation of C4 by-products from ethylene produc-tion. The latter method is principally used today because of the increased demand for ethylene.

Process Descriptions

All but one of the 10 SBR plants addressed in the epidemiologic studies had initially started production by 1943; one plant began operations in 1957. Earliest pro-duction was by batch process. Potassium persulfate and dodecyl mercaptan were used to initiate the poly-merization reaction that occurred at a temperature of about 50°C (8). Hydroquinone was employed to stop the polymerization and N-phenyl-2-naphthylamine was used to stabilize the latex product.

Two major process developments occurred during the early years of SBR production. The first refinement, and perhaps the most important of the two in terms of exposure potential, was the development of a continuous feed system for the polymerization step. This increased production capacity and decreased the need for opening and closing the reactor system. By May of 1948, con-tinuous polymerization was in operation at all of the larger plants (10). The second refinement was based on the discovery of polymerization initiators, such as dia-zothioethers that allowed the polymerization to be car-ried out at temperatures of 5°C and below. The first

large-scale production of cold rubber, that is, SBR pro-duced at low reaction temperatures, was carried out in February of 1948 (10). This development generally fol-lowed the conversion to continuous processes. For ex-ample, in one of the plants studied by Meinhardt et al. (4), conversion to a continuous feed system occurred in 1946, while cold rubber production began in 1949. Plant modernizations have taken place over the years, but the basic processing steps have remained unchanged.

The 1,3-butadiene production process studied by Downs et al. (7) was operated in an entirely enclosed system since the plant opening in 1943. The process was converted from a catalytic to an oxidative dehydrogena-tion process in 1975. A detailed description of the pro-cess is contained in an appendix to the published report (7). This plant had the highest rated capacity of any existing butadiene facility in 1945 (9).

Study Populations

For each of the three epidemiologic studies, eligible employees were determined from a review of personnel records at the facilities (4,6,7). The availability of rec-ords and criteria for selection varied across plants within studies and varied among studies. A brief summary of major selection features is given in Table 1. Minimum employment requirements ranged from 6 months to 1 year, depending on cohort. The period of observation ended between 1976 and 1985. Nevertheless, the maxi-mum observation period for each study was at least 33 years. Cohort identification in the SBR studies extended into or through 1976, whereas cohort identification for the monomer production facility extended through 1979. Women were excluded from all three studies and non-white men were excluded from the smaller of the two studies of SBR employees. This latter study also ex-cluded managerial and administrative only personnel.

Additional restrictions were necessary due to inade-quacies in record systems or other problems of obtaining complete records. In cohort 2, plant B changed owner-ship and was not in operation for 3 years before 1950 (4). Prior records could not be obtained, hence cohort identi-

Table 1. Descriptions of three study cohorts used in 1,3-butadiene evaluation.

| Descriptive variables | SBR studies[a] | | Monomer study |
	Cohort 1 (11)	Cohort 2 (4)	Cohort 3 (12)
Number of facilities	8	2	1
Size of population	12,110	2,756	2,582
Years of observation	1943–1982	1943–1976[b]	1943–1985
Minimum employment required	1 year	6 months	6 months
Employee exclusions	Women	Women, nonwhites, managerial, and administrative	Women
Restrictions due to incomplete records	Left-censoring 4 plants prior to 1953, 1958, 1964, 1970; in one plant employees under age 45 with < 10 years employment	Left censoring one plant prior to 1950	

[a]SBR, styrene-butadiene rubber.
[b]Preliminary vital status follow-up completed through 1982.

fication began in 1950. This cohort was thus subject to left censoring. In cohort studies left censoring occurs when otherwise qualified individuals are lost to study because of missing information at the beginning of their observation period. Right censoring results from individuals becoming lost to follow-up after qualification for the study.

In the larger SBR study, four of the facilities were similarly subject to left censoring, as employee records of former employees were not retained until 1953, 1958, 1964, and 1970, respectively (11). Thus, only a portion of the total worker population employed prior to these dates could be identified for study. Finally the Canadian plant was subject to an additional restriction. Since vital status follow-up could only be completed for vested employees, the Canadian subcohort was restricted to men with 10 years of employment or who had reached age 45 before termination. The population sizes for the three studies were 12,110 and 2,756 for the two SBR studies and 2,582 for the monomer plant study (4,11,12). These statistics reflect the studies as updated in 1988. The study populations were predominantly selected from the Gulf Coast region since the facilities for both of the smaller studies were located in Port Neches, TX, and six of the eight plants included in the larger SBR study were located in Texas (four plants) and Louisiana (two plants). However, the Texas plants contributed only about a third of the workers to the larger SBR study.

Assessment of Exposure

Industrial hygiene data were not available for the facilities covered by these studies until the 1970s. Therefore, exposure potential has been categorized based on knowledge of the substances used in the processes and their physical and chemical properties, process descriptions, job descriptions, and the limited industrial hygiene data available after 1975.

From process descriptions, it is apparent that 1,3-butadiene and styrene were the primary process materials in the SBR facilities and that 1,3-butadiene and n-butene were the dominant substances in monomer production. Other chemicals were generally used in much smaller quantities as initiators (potassium persulfate, diazothioethers, paramenthane hydroperoxide, sodium formaldehyde sulfoxylate, and dodecyl mercaptan), regulators (hydroquinone, N-phenyl-2-naphthylamine, and diphenylamine), and product modifiers (carbon black, aromatic extender oils, and other materials). Furfural was used in isolating and purifying the finished product in the 1,3-butadiene monomer facility and pilot plants in the SBR facilities may have produced smaller quantities of a variety of other synthetic rubbers.

Study participants may have worked in other company operations or have been employed elsewhere in other related work activities. This is particularly true for short-term employees. There is evidence of crossover between the 1,3-butadiene monomer facility and the two SBR facilities that it served, even though different companies owned the plants. Approximately 120 men were found to have worked in both the monomer manufacturing facility and one of the SBR plants, including one man diagnosed with leukemia (12).

The general approach used in the three studies to define exposure subgroups was to assign individuals to broad work area categories based on job assignment information. In the smaller of the SBR cohorts (4), the only subgrouping of employees was by their employment date. Those men hired prior to the end of 1945 were separately identified for analysis. This date roughly coincided with the conversion of the production process to a continuous feed operation. Job assignment data were not discussed in detail; however, the cohort was limited to nonmanagerial and nonadministrative personnel. Summary industrial hygiene data, collected at the time of the study, were presented for 1,3-butadiene, styrene, and benzene. Styrene concentrations in both plants were below 15 ppm time-weighted-average (TWA); 1,3-butadiene concentrations averaged 13.5 ppm across samples; and benzene concentrations were below 1 ppm. Benzene was not known to have been used in the facility, but monitoring was done because of an *a priori* concern regarding two leukemias at the facilities.

In the two remaining studies, work area or exposure categories were defined based on job assignments. In the larger SBR study (11), four categories were employed: production, utilities, maintenance, and miscellaneous (laboratory and quality control, research and development, administration, warehouse and shipping, and other plant support personnel). In the monomer facility, exposure was categorized as low (utilities, certain skilled craftsmen, office and management), routine (production workers, laboratory workers, and chemical distribution workers), nonroutine (skilled maintenance and fire department employees), and unknown (truck drivers, supervisors, and engineers). No subcategorization of production employees was provided in either study. These latter two studies addressed duration of employment and latency considerations as well as broad work areas.

The common element across the three studies is the large-scale use of 1,3-butadiene in the facilities being studied. Recognition of the presence of multiple chemical agents is indicated. However, the multiple agent issue was not considered in any proposed exposure classification. A table of 8-hr TWA exposure data for 1,3-butadiene in the SBR industry was included in the IARC review document (5). The observations were based on personnel samples collected from 1976 to 1981 and were presented by job assignment. Some of the measurement data may have been based on total C4 compounds present in the sample, rather than having been specific to 1,3-butadiene.

The available industrial hygiene data were examined to determine if the distributions of exposure concentrations by job corresponded to what is known about the nature of the jobs and their relationship to the SBR

Table 2. Eight-hour, time-weighted-average exposures in SBR[a] plants, 1976–1981.

Job grouping	Number of samples	Percent distribution of samples			
		0–5 ppm	5.1–10 ppm	10.1–25 ppm	25.1 ≥ ppm
1[b]	1886	97	2	1	1
2[c]	847	84	7	5	4
3[d]	794	76	8	8	8
4[e]	259	42	5	12	41

[a]SBR, styrene-butadiene rubber.
[b]Foreman, charge solution makeup, vessel cleaners, waste treatment, finishing operators, warehousemen.
[c]Lab analysts, maintenance crafts (nonroutine).
[d]Stripping-column operators, reactor operators.
[e]Tank car loaders/unloaders.

process. Since 1,3-butadiene is a very volatile gas, potential exposures would be anticipated to be highest during transfer operations and would be expected to be higher in the polymerization than in finishing areas of the plant.

The measurement data are summarized in Table 2 by four job groupings. There are readily apparent differences in the distribution of 1,3-butadiene concentrations across job groupings. For job group one, 97% of the sample readings were below 5 ppm TWA; for each job in their grouping at least 90% of the readings were below 5 ppm TWA. The jobs themselves are primarily distributed in the finishing area of the process. These included coagulation operators, dryer operators, baler and packing operations, and warehousemen. Charge solution makeup occurs before the reaction stage and thus would be expected to present a low opportunity for exposure to 1,3-butadiene. Foremen and vessel cleaners were also assigned to job group one because of the low frequency of readings over 5 ppm TWA. Foremen might be expected to spend time in both polymerization and finishing areas of the plants and to be involved in other supervisory, training, and trouble-shooting activities. Vessel cleaners are responsible for cleaning the reactors after the polymerization step has been completed. Without additional knowledge of the work practices related to this activity, it is not evident why exposure readings experienced in this job are so low, and it is not known whether exposures related to this activity were higher in earlier years.

The second job grouping included individuals assigned to nonproduction jobs who may have been exposed to 1,3-butadiene on a nonroutine basis. For example, individuals in various maintenance crafts would have worked in the SBR production areas on an as-needed basis. Similarly, quality assurance personnel may have been exposed during 1,3-butadiene sample collection and processing but not necessarily at other times during the day. What is not evident from the industrial hygiene data is whether or not sampling was performed only on those occasions when the individual was involved in butadiene-related activities.

The third job grouping included reactor and stripping-column operators. These operators were assigned to the polymerization area or the area in which unreacted monomers were removed and recovered. As indicated in Table 2, these jobs were associated with a greater opportunity for 1,3-butadiene exposure than jobs in the finishing area. The fourth job grouping was made up of jobs involving 1,3-butadiene transfer operations. Highest exposure concentrations have been measured for these jobs, consistent with expectation. The available data do not indicate whether or not respiratory protection was worn during these activities. What is also not known from these or any other extant data is the secular trends in 1,3-butadiene exposure prior to the 1970s. It does appear that the processes themselves have not changed greatly.

Findings across Studies

Cancer mortality findings for the three major cohort studies of 1,3-butadiene workers are summarized in Table 3. Observed and expected numbers of deaths and standardized mortality ratios (SMRs) are presented for selected cancer sites. In each study, the investigators had calculated expected deaths by applying age-specific U.S. death rates to the corresponding distributions of person years lived for the respective cohorts.

The SMR is frequently used to describe mortality in occupational cohorts and is calculated simply as the ratio of observed to expected deaths. For ease of presentation, the SMR has been expressed as the ratio multiplied by 100. The choice of the U.S. general or other community-based population as the referent group for an employee population has been criticized based on the recognition that initial and ongoing selection of healthy men may lead to relatively lower death rates in the occupational cohort. This issue is less critical when the period of observation is long, the follow-up of terminated employees is complete, the mortality ratios are examined relative to interval since first employment, and comparisons to the mortality experience of other employee-based cohorts are made.

Aside from the selection issue, there are two weaknesses of the SMR that need to be kept in mind when interpreting mortality findings. First, an SMR can be misleading when the implied assumption of a constant proportional hazard is not true for all population subgroups. In other words, there may be risks not reflected in the summary SMR because of the dilution of effects specific to a particular group of employees. In practice,

Table 3. Mortality findings for three 1,3-butadiene studies.[a]

	SBR plants				Monomer plant	
	Cohort 1 (*11*)		Cohort 2 (*4*)		Cohort 3 (*12*)	
Cause of death category	O/E	SMR	O/E	SMR	O/E	SMR
All causes	2441/3001	81	332/430	77	826/980	84
All cancer	518/606.7	85	56/78.1	72	163/202.7	80
Total digestive	158/169.1	93	13/22.4	58	39/56.3	69
Esophagus	17/16.9	100	NR		3/4.8	[b]
Stomach	34/32.5	105	NR		4/10.2	39
Respiratory	177/209.8	84	21/24.6	85	57/69.8	82
Brain and other central nervous system	14/17.3	81	NR		4/5.7	70
All lymphopoietic	55/56.7	97	11/8.3	133	25/19.2	130
Leukemia	22/22.8	96	6/3.5	171	8/7.9	102
Hodgkin's disease	8/6.6	120	1/1.4	[b]	3/2.1	
Lymphosarcoma	7/11.5	61	4/2.4	[b]	9/3.9	229
Other lymphatic tissue	17/15.4	111	0/1.1	[b]	5/5.1	97

[a]Abbreviations: SBR, styrene butadiene rubber; O, observed; E, expected; SMR, standardized mortality ratio; NR, not reported.
[b]Fewer than five observed and five expected deaths.

the solution to this problem is to examine and evaluate separately the mortality findings for key subgroups within the cohort before using summary measures to describe the findings. Homogeneity tests are available for quantitatively evaluating the consistency of risk ratios across strata. A second weakness is that SMRs may lack mutual comparability because each SMR is standardized to its own set of internal stratum weights. Again, this is a problem only to the extent that the assumption of a constant proportional hazard is invalid, again, the broad solution is to examine the detailed findings before using the summary measure. Similar considerations apply to the question of combining mortality data across studies.

Returning to Table 3, it can be seen that the SMRs for all causes of death were relatively consistent across the three studies, the SMRs varying between 77 and 84. Similarly, the SMRs for total cancer deaths varied between 72 and 85. The findings were also relatively consistent and unremarkable for respiratory cancer and cancer of the brain. SMRs were relatively higher for digestive system cancers in the larger SBR cohort (cohort 1) but were similar between cohorts 2 and 3. In fact, the general pattern of mortality findings was quite similar between the two Port Neches cohorts for each cause of death examined.

For cancers of the lymphopoietic system, the distribution of deaths by cancer subcategory differed notably between the larger SBR cohort and the two smaller

cohorts. The largest contrast was seen for lymphosarcoma deaths where the mortality ratio for cohorts 2 and 3 combined (SMR = 206 based on 13 deaths) was more than two times that of cohort 1 (SMR = 61 based on 7 deaths). The difference was less striking when lymphosarcoma deaths were combined with deaths due to other lymphatic tissue cancers. This latter category includes multiple myeloma and other lymphoid tissue neoplasms; the other lymphoid tissue tumors are often grouped with lymphosarcoma under the rubric of non-Hodgkins lymphoma. For all lymphopoietic cancers, mortality was about 30% higher for cohorts 2 and 3 combined compared to cohort 1; however, the number of observations was small and the difference was not inconsistent with a chance occurrence. There were 36 observed and 34.2 expected leukemia deaths across the three cohorts and no remarkable differences between cohorts.

In Table 4, the distribution of observed and expected deaths due to all lymphopoietic tissue cancer is presented by length of employment in the industry and latency (interval since hire) for cohorts 1 and 3 combined. Comparable data were not available for cohort 2. The SMRs increased slightly with longer intervals since hire and decreased slightly with longer lengths of employment, but these trends are, for the most part, rather unremarkable.

Observed and expected deaths are summarized for production and maintenance employees in Table 5, again combining cohorts 1 and 3. The work area categories are

Table 4. Distribution of observed and expected deaths by length of employment and latency for all lymphopoietic cancer for cohort 1 and cohort 3.[a]

	Latency, years							
	<10		10–19		20+		Total	
Length of employment, years	O/E	SMR	O/E	SMR	O/E	SMR	O/E	SMR
<10	7/8.4	83	5/6.6	76	23/16.5	139	35/31.6	111
10–19			14/12.5	112	10/6.5	154	24/19.0	126
20+					21/25.2	83	21/25.2	83
Total	7/8.4	33	19/19.1	99	54/48.2	112	80/75.8	106

[a]Abbreviations: O/E, observed/expected; SMR, standardized mortality ratio.

Table 5. Observed and expected deaths by cause for production and maintenance employees for cohort 1 and cohort 3 combined.[a]

Cause of death category	Production		Maintenance	
	O/E	SMR	O/E	SMR
All causes	757/890	85	1298/1445	90
All cancer	166/182	91	257/290	89
Total digestive	37/49.2	75	73/83.3	88
Esophagus	3/4.8	[b]	6/7.9	76
Stomach	5/9.0	56	19/16.3	138
Respiratory	63/64.1	98	92/97.9	94
Brain and other central nervous system	3/5.6	54	5/7.4	68
All lymphopoietic	27/17.5	154	25/26.4	95
Leukemia	8/7.0	114	12/10.8	111
Hodgkin's disease	3/2.3	[b]	4/2.8	[b]
Lymphosarcoma	6/3.5	171	4/5.3	75
Other lymphatic tissue	10/4.7	213	4/7.2	56

[a]Abbreviations: O/E, observed/expected; SMR, standardized mortality ratio.
[b]Fewer than five observed and five expected deaths.

approximate since the production group in cohort 3 includes laboratory personnel and 1,3-butadiene-distribution employees. The SMRs for all causes of death and total cancer deaths are similar in both employee groups and are somewhat above the comparable SMRs for the total cohort. The stomach cancer SMR is relatively higher in the maintenance work group than in the production work group; for lymphopoietic cancer the reverse is true. The overall lymphopoietic cancer pattern reflects the differences in lymphosarcoma and cancer of other lymphatic tissue between the two groups. The SMRs for lymphosarcoma and cancer of other lymphatic tissue are 171 (based on 6 deaths) and 213 (based on 10 deaths) in the production group, and they are 75 (based on 4 deaths) and 56 (based on 4 deaths) in the maintenance group. The larger SBR cohort contributed 9 of the 10 observed deaths due to other lymphoid tissue cancers in the production group, whereas the monomer cohort contributed 5 of the 6 observed lymphosarcoma deaths in the production group. The mortality ratios for leukemia and Hodgkin's disease were nearly the same for production versus maintenance employees and did not differ from the ratios observed in the combined population of the three studies.

Discussion

The mortality experience of over 17,000 men employed in the synthetic rubber industry or in a 1,3-butadiene monomer producing facility has been examined in three large retrospective cohort studies (4,11,12). In each study the period of observation exceeded 30 years. Overall and total cancer mortality were rather unremarkable in the combined populations from these studies. The corresponding SMRs were comparable to those observed in similar long-term studies of men working in the petroleum, chemical, and rubber industries (13–21). Likewise, the SMRs for total lymphopoietic cancer and leukemia of 108 and 105 were consistent with the range of SMRs, 95 to 110 and 88 to 118, respectively, observed in other long-term occupational studies (13–21). These

cancer sites were targeted for review because of an increased occurrence of lymphomas observed in B6C3F$_1$ mice, relative to 1,3-butadiene exposure (1). Hemangiosarcomas of the heart and other proliferative lesions of the lung and forestomach were also reported in the mouse bioassay.

In general, there were no remarkable mortality findings relative to the cancer sites examined for the three cohorts viewed together. Furthermore, a combined analysis of the large SBR cohort and the monomer cohort by length of employment in the facilities and interval since hire failed to provide evidence of a relationship between total lymphopoietic cancer and these factors. Thus, the overall pattern of findings does not indicate that untoward mortality effects have occurred in the studied populations. Nevertheless, an assessment of the carcinogenicity of 1,3-butadiene based on the combined data alone is less than satisfactory. There may be dilution effects across the studies since the cohorts included both production and production support personnel whose exposures to 1,3-butadiene may have been minimal and there have been no analyses based on exposure intensity.

Several discrepant findings were observed in more detailed analyses within individual cohorts and employment subgroups. Among the individual cohorts, there was an increased number of deaths due to lymphosarcoma in cohorts 2 and 3, the two Texas cohorts. For cohort 3 analyses, Downs et al. (7) provided mortality comparisons to both a seven-county region of southeast Texas and the general U.S. population. These data indicated that the regional death rates for lymphosarcoma were about 30% higher than the corresponding national rates. This regional difference is too small to account for the total excess of lymphosarcoma deaths observed in cohorts 2 and 3. However, when considered in the context that regional death rates for other lymphatic tissue cancers were lower for southeast Texas than for the rest of the nation, these data suggest that geographic factors play a role in the distributional differences of lymphopoietic tissue cancers seen among the cohorts.

This observation also draws attention to the question of the reliability of the death certificate diagnoses within the lymphopoietic system. Detection and confirmation rates are reasonably good for major subcategories such as leukemia and non-Hodgkin's lymphoma, but are lower for more refined subcategories, for example, myeloid leukemia and monocytic leukemia (22). In general, difficulties in obtaining accurate diagnoses would be expected to obscure underlying relationships between exposure and disease outcome. While efforts to confirm diagnoses for deaths within the lymphopoietic cancer category may be helpful, this approach does not address the underreporting aspects of the issue.

An interesting observation in the Meinhardt et al. (4) study was the short latency period reported for three of the six qualifying leukemia cases and the early hire date of the cases. The interval between first hire and death due to leukemia was 3 years in two cases and 4 years in one case. Two of these decedents had first been employed in the plant prior to 1945, as had the remaining three leukemia decedents with longer intervals between hire date and death. In the remaining two cohorts, only one additional leukemia death was observed with a latency period of under 10 years. This decedent had been hired in 1976. Thus the unusual pattern observed in one cohort relative to interval since hire was not repeated in the other two studies. The larger SBR study did not provide tables to examine separately the leukemia experience of men hired during the early years of operation and therefore, early hire date could not be evaluated across studies.

Mortality comparisons between two broadly defined job activity groups, production and maintenance, identified differences in death rates for several categories. In particular, lymphopoietic cancer death rates were relatively higher among production employees; stomach cancer death rates were relatively higher among maintenance employees. Within the lymphopoietic cancer category, highest SMRs for production employees were observed for lymphosarcoma and other lymphatic tissue cancers. Because production employees may include individuals with potential 1,3-butadiene exposures less than as well as greater than the exposures of maintenance personnel, one can only speculate as to meaning of these data relative to 1,3-butadiene.

Additional efforts to refine the measures of 1,3-butadiene exposure and to develop a more comprehensive assessment of other exposures in the SBR industry would be helpful in more precisely evaluating the mortality findings from these three studies. Continuing efforts to update the existing studies are also needed. In the interim, these studies do not provide convincing evidence that links adverse mortality effects to 1,3-butadiene exposure.

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